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(54) MEDICINAL COMPOSITIONS CONTAINING CAMPTOTHECIN DERIVATIVE AND PH REGULATING AGENT

(57) A pharmaceutical preparation which ensures stability and solubility of a haxacyolic campotihecin derivative prepared by adding a ring having a water-soluble group to camptothecin, wherein a pH-adjusting subble group to camptothecin. stance and, as occasion demands, a sugar or a sugar alcohol are added to the hexacyclic camptothecin derivative.

#### Description

Technical Field

5 [9981] This invention relates to a pharmaceutical composition containing a camptothecin derivative.

#### Background Art

[0002] The camptotheon anti-tumor agents so far put on the market were aqueous injections produced by an overkill starlizing method (retainent at 121°C for 20 minutes). However, in the case of a hexacyclic camptothecin derivative in which a ring having a water-soluble group is added to camptothecin, it has been revealed that the compound is degraded when similar overkill approach is carried out.

[0003] The invention provides a pharmaceutical composition which ensures stability and solubility of a hexacyclic camptothecin derivative in which a ring having a water-soluble group is added to camptothecin.

#### Disclosure of the Invention

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[9004] As a result of intensive studies, the present inventors have found that stability of a hazacyclic camptothecin cervative in which a ring having a water-soluble group is added to camptothecin, particularly (93)-timeno-district S-fluoro-2.3-dilhydro-9-rystroxy-4-methyr-11.12H-benzo(leighyrand)3.4\*(o,7)molitizing)1.2-bylanibin-10,13(91,13)-13(1)-13

[0005] Accordingly, the invention relates to a pharmaceutical composition which contains a camptothecin derivative

and a pH-adjusting substance.

[0006] Particularly, it relates to a pharmaceutical composition which contains (9S)-1-amino-6-athyl-5-fluoro-2,3-di-

hydro-9-hydroxy-4-methyl-11-12H-benzo(de)pyrano(3:49-5,7[indollizino(1-2-0]quinoline-10,13(9H, 15H) -dione or a salt thereof (it may form a hydrate or the like solvate) and a pH-edjusting substance.

[0007] Also, it relates to a pharmaceutical composition which contains (\$5)-1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-mathyl-1H-1,2H-benzo(de)pyrano(3',4':8.7]indollizino(1,2-b]quinoline-10.13(9H,15H)-dione or a salt thereof and hydrochieric solid.

[0008] Further. It relates to a pharmaceutical composition which contains (9S)-1-amino-9-ethyt-5-fluoro-2.3-shydro-9-hydroxy-4-methyl-1H.12H-benzqdelpyrano[3:45]-flindoixinof[1.2-bjquinoline-10.13 [9H.15H] -dione or a sall thereof, a pH-adjusting substance and one or more of sugars and/or sugar alcohos selected forms the group consisting of maitose, glucose, lactose, saccharose, mannitol, inestiol, galactose, ribose, xylose, mannose, sucrose, celiobiose, rafilinose and meliotiose.

[2005] Also, il relates to a pharmaceutical composition which contains (9S)-1-ardino-9-ethyl-6-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(de)pyrano[3,4:5.7]indoizino[1,2-diquinoline-10,13(9H,16H)-dione or a salt there-of, hydrochloric acid and one or more of sugars and/or sugar actionles selected from the grupo ponsisting of materials, glucose, lactose, saccharose, mannitol, inositol, galactose, ribose, xylose, mannose, sucrose, cellobiose, raffinose and maltotical

[0010] Further, it reliates to a pharmaceutical composition which contains (98)-1-emino-6-eithyl-5-fluoro-2.8-dihydro-9-hydroxy-4-methyl-1H.12H-benzo[de]gyrano[3,4-6,7]indoilizho[1,2-b]quinoilin-1(3), (9H,16H) -dione or a satistic result of the properties of the p

[0011] Also, it relates to a pharmaceutical composition which contains (8)-1-dernino-9-athyl-5. Buero-2,9-dihydro-9-hydrocy4-enthyl-11,1241--bearzo(de)pyrano(3,4-6.7)indeizmo(1,2-b)quindine-10,13 (9H.15H) -dione or a satt thereof, a pH-adjusting substance and one or more of august and/or sugar alcohols selected from the group consisting of matiose, glacose, lactose, saccharces, manniol, inosticil, galactices, ricose, zylose, mannose, sucrose, ocitobiose, crisinose and materinose, wheren blending amount of the sugar and/or sugar alcohol is from 25 to 75 parts by weight based on 1 part by weight of (95)-1-amino-9-othyl-5-fluoro-2,3-dihydro-9-hydroxy-4-metryl-1H,12H-benzo[de]pyrano [2,4-6];7/miodicino[1,2-b]quinoine-10,1(9H.15H)-dine or a satt thereof.

[0012] Further, it relates to apharmaceutical composition which contains (9S)-1-amino-6-ethyl-5-fluore-2,3-dihydro-6-hydroxy-4-methyl-14,129t-benz(dialpyrano[3-4/5,7]moloizinnd [2-blq/imoline-10.13(9H,16H)-dione or a sall there-of-hydrochlore acid and one or more of sugars and/or sugar alcohols selected from the group consisting of matitose, plucose, lactose, saccharose, mannitel, invisted, galactose, ribose, xylose, mannese, sucrose, celiobiose, raifinose

and maticinose, wherein blanding amount of the sugar and/or sugar alcohol is from 16 to 80 parts by weight based on 1 part by weight of 1951-amilno-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzoldejpyrand[3',4':6,7] and/ol/pind[1-9-hightholino-10-316]https://doi.org/10.116

[0013] Alno, it relates to a pharmaceutical composition which contains (SS)-1-amino-9-ethyl-5-fusoro-2-dishydrob-hydroxy4-methyl-1+, 12t-benzofelplyman(3/4-5) filindoising (1-2-a)quanoline-1-0,13(9H,15th)-done or a sett thereof, hydrochloric acid and one or more of sugars and/or sugar alcohols selected from the group consisting of matters, plucose, lactose, saccharose, mannich, inasted, glactose, riloses, xylose, mannose, sucrose, ceitibioses, refinose and matiofrose, whereith biending amount of the sugar andros usugar alcohols from 25 to 75 parts by weight beach or 1 part by weight of (SS)-1-amino-9-cityl-6-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(de)pyrano[3/4/5,7] indoizion[1-2-blumbille-0-1-3(9H,15f)-bidnoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(de)pyrano[3/4/5,7] indoizion[1-2-blumbille-0-1-3(9H,15f)-bidnoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(de)pyrano[3/4/5,7]

[0014] Further, it relates to a pharmaceutical composition which contains(9S)-1-amino-9-athyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(be)pyrano(3',4''5,7|indoiizino(1,2-b)quinoline-10,13(9H,15H)-dione or a salt there-of, thydroblinfo acid and matthse.

[0015] Also, it relates to a pharmacoulical composition which contains (9S)-1-amno-9-ethyl-5-fluoro-2,3-dihydro--hydroxy-4-methyl-1-h,12H-bonzo(dejpyrano[3,4's,7jindolizino[1,2-b]quinoline-10,13(6H,15H)-dione or a sait thereol. hydrochione acid and maltosa, wherein blending amount of maltose is from 15 to 80 parts by weight losed on 1 part by weight of (9S)-1-amino-9-othyl-6-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(dejpyrano[3,4':5,7jin-dolizino[1,2-b]quinoline-10,13(ght,15H)-dione or a sait threeof.

[9016] Further, it relates to a pharmacoutical composition which contains (59)-1-arrino-9-ethyl-1-fulcor-2.3-dihydro-9-thydroxy-4-methyl-1-H,12H-benzo(de)pyrano(3;4':8.7]indolizino(1,2-b)quinoline-10,13(9H,15H)-dione or a sati there-of, hydrochlotic acid and matiose, wherein blending amount of matiose is from 25 to 75 parts by weight based on 1 part by weight of (65)-1-amino-9-athyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':6.7]indolizino[1,2-b]bulanoine-10,3(9H,15H)-indoor or a sati thereof.

[0017] Also, it relates to a pharmacoutical composition which contains (9S):1-amino-9-citryl-6-fluoro-2,3-dftrydro-9-hydroxy-4-methyl-1H-12H-benzo(de)pyrano[3/4-8/7]ndollzino[1,2-b)quinoline-10,13(9H,15H)-dione hydrochloride or methanesullonate, hydrochloride and mailtose.

[0018] Further, It relates to a pharmace-autical composition which contains (93)-1-amino-9-athyls-fluore-)g-drihydroshydroxy-4-methyl-1H,12H-benzo(de)gyrano[3]-4'-5,7]indoizino[1,2-bjquinoline-10,13(9H,15H)-dlinore-)g-droinoride or methanesuflonate, hydrochloric acid and matose, wherein blending amount of matose is from 15 to 80 parts by weight based on 1 part by weight for (95)-1-amino-9-drihy-5-fluoro-2,3-drihydro-9-drydroxy-4-methyl-1H,12H-benzo[de] ovarano[3'-4'-5]: findoizino[1-2-bjulinoline-10-10](9H) 15H-dlinore hydroxhofidd or methanesuffloration

[0019] Also, it relates to a pharmaceutical composition which contains (3S)-1-amino-9-ethyl-5-fluoro-2\_3-dirydro-9-hydroxy-4-methyl-1H, 12H-benzo(de)pyrano(3', 4': 6.7]holdizinof1,2-blquinoline-10,13(9H,15H)-dions hydrochioride or methanesultonate, hydrochloric acid and maltiose, wherein blending amount of maltiose is from 25 to 75 para by weight based on 1 part by weight of (9S)-1-amino-6-ethyl-5-fluoro-2\_3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo (de)pyrano(3',4':5.7]holdizinof1,2-blquinoline-10,13(9H,15H)-fluoro-2\_3-dihydro-9-mydroxy-4-methyl-1H,12H-benzo (de)pyrano(3',4':5.7]holdizinof1,2-blquinoline-10,13(9H,15H)-fluoro-2\_3-dihydro-9-mydroxy-4-methyl-1H,12H-benzo

[0020] Further, it relates to a pharmaceutical composition which contains (1S.9S)-1-amino-9-sithyl-5-fluoro-2,3-dihydro 9-hydroxy-4-methyl-1H,12H-decopde[pyrano[3,4:6,7]indoilizino[1,2-b]quinolino-10,13[9H,15H]-dione or a sait thereof end a Ph-aditisating substance.

60211 Also, it relates to a pharmacoutical composition which contains (15,95)\*1-amino-9-athyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(dejpyrano[3\*,4\*:6,7]indoilzino(1,2-b]quinoline-10 13(9H,15H)-dione or a satt thereof and hydrochlore acid

[0022] Further, it relates to a pharmaceutical composition which contains (15,85)-1-amino-9-ethyt-5-fucioro-2,3-dity-dro-9-hydroxy-4-methyt-1H, 12H-benzo(de)pyrano(3,4:6.7)indolfzino(1,2-b)quinotine-10,13(9H, 16H)-5-fucior or a self-thereof, a pH-adjusting substance and one or more of sugars and/or sugar achorbs sevected from the group consisting of maliose, glucose, lacrose, sacoharose, mannitol, inositoi, galactose, ribose, xylbse, mannose, sucrose, cellobisse, rafilinose and malioulisse.

[9023] Also it relates to a pharmacoutical composition which contains (15,96)-1-amino-9-ethyl-5-fluoro-2,3-dilydro-9-hydroxy-4-methyl-114,124-benzoldelpyrano[3',4',5,7]indoizino[1,2-o]quinoline-10,13(9H,15H)-fdione or a sati ihered, hydrochloric acid and one or more of sugars anafor sugar alcohols selected from the group consisting of malicae, gluoce, jactose, saccharose, mannitol, inositol, galactose, ribosa, xylosa, mannise, sucrose, cellobicae, rafilmosa and maliotrose.

[0024] Further, it reletes to a pharmacourized composition which comains (15,95)-1-amin-q--orthyl-6-fluoro-2,3-ditydro-9-hydroxy-4-methyl-1H.12H-benzo(dejpyrano)3,4-8,7[indoixino]1.2-biquinoine-10,13 (9H.15H)-10ione or a sait hereof, apth-adjusting substance and one or more of sugars and/or sugar alcohols selected from the group consisting of maltose glucose, lactose, saccharose, mannitol, inostiol, galactose, ribose, xylose, mannose, sucrose, celiobiose, raffirose and matorifose, wherein blanding amount of the augar and/or sugar alcohol is from 15 to 80 parts by weight based on 1 part by weight of 1951-1 aminos-9-4th-5-fluoro. 2-of chirdros-9-thydrox-4-methyl-1H-12-the-parzidelelowanc

[3',4'-6,7]indolizino[1,2-b]quinoline-10,13(9H,15H)-dione or a salt thereof.

[0026] Alzo, It relates to a pharmaceutical composition which contains (15.98)-1.samno-9-ethyl-5-fusor-2.3-dilydre-9-hydroxy-4-multy-1-ft.21-b-parano(3-7-8.7)moltizing 1.2-blguinoline-10.13 (9H.15H) -dione or a sait thereof, apH-adjusting substance and one or more of sugars and/or sugar alcohols selected from the group consisting of matiose, glucose, lacciose, secharose, miannilo, inostio, galactose, ribose, xylose, manose, sucross, cellobiose, reliferose and matoriories, wherem blending amount of the sugar and/or sugar alcohols is from 25 to 75 parts by weight based on 1 part by weight of (95)-1-amino-9-ethyl-5-fusor-2.3-dilydro-9-hydroxy-4-methyl-1H,12H-bonz-q-delpyario (3-4/8-f)/nolinion-[1.3-2]-hydros (15H-dono) or a satt thereof.

[9028] Further, it relates to a pharmaceutical composition which contains (18,98)-1-amino-9-ethyl-6-fluoro-23-dilyrdro-9-hydroxy-4-methyl-14.124-bearze(de)pyrano(3',4'6.7]indolzino(1,2-b[quinotine-10,13(2H-15H)-dicton or a sat thereof, hydrochloric acid and one or more of august and/or sugar atcohols selected from the group consisting of mattess, glucose, lactose, saccherose, marnitol, incelloi, galectose, ribose, xylose, mannose, sucrese, celibolises, ratifinose and maitoritose, wherein bloading amount of the sugar and/or sugar aclonol is from 15 to 80 parts by weight based on 1 part by weight of (98)-1-amino-9-ethyl-5-fluoro-23-dihydro-9-hydroxy-4-methyl-14,12H-benzo(de)pyrano 13,4'e5,7/indoltzmolf\_2-bloationise-10,13(9H,16H)-done or satil thereof.

[0027] Also, it relates to a pharmaceutical composition which contains (15,98)-1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1+1,12H-benzo[de]byrano[3] 4;5,7 jindolzino[1,2-bjunioline-10,199H,15H)-dione or a self thereof, hydrochloric acid and one or more of sugars and/or sugar shoohs selected from the group censisting of makingglucose, lactose, sacoharose, mannitel, incettot, galeciose, ribose, prannose, sucrose, celiobiose, raffinese and maliotiose, wherein bending amount of the sugar and/or sugar sachol is from 25 to 75 parts by weight based on 1 part by weight of (69-1-amino-9-sttyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[9],4'-6.7] indolzino[1,2-9]quipinioi-19,19(9)H-15H-binoro or a self thereof

[0028] Further, it relates to apharmaceutical composition which contains (15,95)-1-amino-9-eithyl-5-fluoro-2,3-dillydro-9-hydroxy-4-mittyl-111,12H-benz(deljpyrano[3,4%6.7]indoizino[1,2-b]quinoline-10,13(8H,15H)-diene or a satt thereof, hydrobihoria edid and mattees.

[0029] Also, it relates to a pharmaceutical composition which contains (15,96)-1-amino-9-ethyl-5-fluoro-2,9-dihydro-9-hydroxy-4-methyl-1-H,124-benzo(elpyarend)-4,4:9-[7]medizine(1,2-e)quinoline-10,13(9H,16H)-dione or a salt there-0, hydrochlore acid and meticse, wherein blending amount of meticse is from 15 to 80 parts by weight based on 1 part by weight based by weight based on 1 part by weight based on 1 part by weight based on 1 part by weight hased on 1 part by weight based on 1 part by weight based on 1 part by weight based on 1 part by weight hased on 1 part by weight has 2 part by weigh

[0030] Furtner, it relates to a pharmaceutical composition which contains (15,65)-1-amino-9-ethyl-5-fluoro-2,3-dmy-dros-9-hydroxy-4-nethyl-11,12H-benzo(de)pyrano(3,4'8,7)indoizino[12-b]quinolino-10,13(6'1,15H-dione or a satt thereof, hydrochloric sold and mattose, wherein blending amount of mattose is from 25 to 75 parts by weight based of 1 part by weight based on 1 part by weight based on 1 part by weight sold (95)-1-amino-9-ethyl-6-fluoro-2,3-diffycin-9-hydroxy-4-methyl-11,12H-benzo(de)pyrano[3,4'8.7] indoizino[1,2,9]uinoline-10,13(9)H-15H-dione or a satt ihrency

[0031] Also, it relates to a pharmaceutical composition which contains (15,95)-1-amino-9-ethyl-5-fluoro-2,3-dhydro-9-hydroxy-4-methyl-1H.12Fl-benzqide)pyran(3,4:5,7]/indoizino(1,2-b)quinotine-10,13 (9H,15H)-dione hydrochloride or methanesutionatic, hydrochloric acid and mailtose.

[0032] Further, it relates to a pharmaceutical composition which comains (15,95)-1-amino-8-athyl-6-fluoro-2,3-dlhy-dro-9-hydroxy-4-amthyl-11,12H-benzet(de)pyrano(3',4'6,7)indolizinc|1,2-b]quinolin-e-10,13(9+,15H)-dione hydro-phioride or methanesulfonate, hydrochloric acid and mailtose, wherein blanding amount of matices is from 15 to perit by weight based on 1 part by weight of (65)-1-amino-8-athyl-6-fluoro-2,3-dlhydro-9-hydroxy-4-mothyl-11,12H-benzet(absyn-not)-4-in-7)indolizince|1,3-b]quinoi-1-0,13(9H,15H)-dione hydrochloride or methanesulfonate.

[0033] Also, It relates to a pharmaceutical composition which contains (16 [85]) - termino-0-ethyl-6-fuor-o.2,3-dihydro-3-hydrory-4-archityl-tH, 12(1-benzo(de)pyrano(3; 4:6,7)indolizino(1,2-o)quinoline-10,13(9H,16H)-dione hydrochiorise or methenesulfonate, hydrochiorise acid and mailtose, wherein blanding amount of mailtose is from 25 to 75 pans by weight based on 1 part by weight of (95)-1-emino-9-ainyl-6-fluor-o.2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(de) pyrano[5]-6-7-findolizind[5]-2-fiplusinien-10,13(9H,15H)-dione hydrochioride or methanesulfonate

[0034] Further, it relates to the aforementioned pharmaceutical composition, wherein pH is a weakly acidic condition.

[0035] Also, it relates to the aforementioned pharmaceutical composition, wherein pH is from 3.5 to 5.0.

[0036] Further, it relates to the aforementioned pharmaceutical composition, wherein pH is from 4.0 to 4.5.

[0037] Also, it relates to a pharmaceutical composition which contains (98): 1-amino-9-entyl-5-fluoro-2.3 dihydroshydrory-4-mothyl-1H,12H-benzo(dejpyrano(3' 4' 6.7)indolizinof(1,2-b)quinofine-10,13(9H;16H)-dison methanssuitonate, hydrochioric acid and mattose, whereir blanding amount of matiese as 25 or 38 parts by weight based on 1 part by weight of (9S)-1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(dejpyrano(3',4'',8,7)]adolizinof(1-2-b)quinofine-10,13(4),15H-blione methanesut/forata, and of his from 4.0 to 4.5.

[0038] Further, it relates to a pharmaceutical composition which contains (15.95)-1-amino-9-ethyl-5-fluoro-2-3-dihydro-9-hydroxy-4-methyl-1H, 12H-benzo(de)pyrano(3', 4', 6,7)indolizino(1,2-b)quinoline-10,13(9H,15H)-dione meth-

acestificate, hydroctiticite acid and mafines, wherein blending amount of metoses is 25 or 38 parts by weight based on 1 part by weight based on 1 part by weight of (95) -1-emino-9-eithyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-bonzoldelpytranq3'.4' 6 7 [indolzind 1,2-b]quinoline-10.13(9H,15H)-fluore methanosulfonate, and p4 is from 4.0 to 4.5.

[0039] Also, it relates to a freeze-dried preparation which contains the aforementioned pharmaceutical composition.

[0040] Further, il relates to an aqueous preparation prepared by dissolving the above freeze-dried preparation [0041] Alico, il relates to a process for producing the abover-monitoned freeze-dried preparation which comprises adjusting an aqueous solution containing (9S) -1-amino-9-ethyl-5-fluoro-2,3-dihydro-8-hydroxy-4-methyl-1H,12H-bendate-bether prof. (4) of the behavior of (6) this prof. (2) of the prof. (2) of the prof. (3) of the prof. (4) of the prof.

zo(de)pyrano[5].4%6.7[indol/zino(1,2-b]quinoline-10,13(9H,15H)-dione or a salt thereof to a weakly acidic condition, and then freeze-drying the resulting solution.
[0042] Further, it relates to a process for producing the abovementioned freeze-dried preparation which comprises

steps of:

- (1) preparing an aqueous solution by dissolving sugars and/or sugar alcohols in water;
- (2) dissolving (9S)-1-ammo-9-sihyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':6,7] indolizino[1,2-b]quinoline-10,13(9H,15H)-dione or a salt thereof;
- (3) adjusting pH to a weakly acidic condition with a pH-adjusting substance; and
- (4) dispensing the resulting solution into vial after filter-sterilizing it, and followed by freeze-drying it.

[0043] Also, it related to a process for producing the abovementioned freeze-dried preparation which comprises steps of.

- (1) preparing an aqueous solution by dissolving maltose in water;
- (2) dissolving (1S,9S)-1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':
- 6,7)indolizino(1.2-b)quinoline-10,13(9H,15H)-dione methanesulfonate;
- (3) adjusting pH to from 3.5 to 5.0 with a pH-adjusting substance; and
  - (4) dispensing the resulting solution into vial after filter-sterilizing it, and followed by freeze-drying it.

[0044] Further, it related to a process for producing the abovementioned freeze-dried preparation which comprises steps of

(1) preparing an aqueous solution by dissolving mallose in water:

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- (2) dissolving (15,95)-1-amino-9-athyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(de)pyrano(3',4':
- 6.7 indulzing 1,2-bjquinoline-10,13(9H,15H)-dione methanesulfonale;
- (3) adjusting pH to from 4.0 to 4.5 with hydrochloric acid; and
- (4) dispensing the resulting solution into vial after filter-sterilizing it, and followed by freeze-drying it.

[9045] Further, use of (9S)-1-amino-9-ethyl-6-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[d', 4-6,7]/indoikind[1,2-b]quinoline-10,13[9H,15H]-dione or a sall thereof for producing the aforementioned pharmaceuloal composition, freque-dried proparation and acueue or expendant

[0046] Also, use of (15,95)-1-amino-9-ethyl-5-fluoro-2,3-dihydra-9-hydroxy-4-methyl-1H,12H-banzo(de)pyrano[3', 4'.5,7]mdolizinof(1,2-0)qumbits=10,3(9H,16H)-dione methanesulfonate for producing the aforementioned pharma-ceutral composition, freez-dried preparation and aqueous preparation.

[0047] Compound A as the camptothecin derivative in the pharmaceutical composition of the invention can be synthesized by the method described in JP-A-5-69061 (the term "JP-A" as used herein means an "unexamined published Jepanese patent application"). In this connection, when the camptothecin derivative in the pharmaceutical composition of the invention is described as (9S) -1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzolde) pyrano[3',4';6,7]indol.cino[1,2-b]quinoline-10,13(9H.15H) dione or compound A in this description, configuration of the 1-positioned amino group is not particularly limited. When configuration of the 1-positioned amino group of the aforemanifored completnesin derivative is limited in this description, a compound, in which configuration of the 1-positioned amino group is 5 configuration, is described as (15.95)-1-amino-9-ethyl-5-flyoro-2,3-dihydro-9-hydroxy-4-methyl-1H, 12H-benzo(de)pyrano[3'.4'.6,7|indokzino[1,2-b] quinoline-10,13(9H,15H) dione or compound AS, and a compound, in which configuration of the 1-positioned smino group is R configuration, is described as (1R,9S)-1-amino-9-ethyl-5-fluoro 2,3-dinydro 9-hydroxy-4-methyl-1H, 12H-benzofdelbyranof3',4':8, 7lindolizinof1,2-blouinofine-10,13 (9H,15H) -dione or compound AR. Since both of the compound AS and compound AR have potent ant-tumor effect, they can be used as a mixture of both isomers or the compound AS or compound AR alone as a component of the pharmaceutical composition, but single use of the compound AS is particularly desirable because the compound AS has about two times higher anti-tumor effect than their of the compound AR. The compound A (molecular weight, 435) may form a generally known salt, and examples of the salt include hydrochloride, sulfate, phosphate, tosyrate, methanesulfonate

and the like. Especially hydrochloride and mathanesulfonate are desirable. In addition, it may form a hydrate or the like solvate. For exemple, methanesulfonate dihydrate and the like are ofted and it can be prepared by the method described in JPA-8-0-37584.

[0048] The compound A or a salt thereof in the pharmaceutical composition of the invention is used in an amount sufficient for expressing the drug effect, and it is extinitistered at a dose within the range of from about 0.01 mg to about 10 mg, proferably from about 0.1 mg to about 6 mg, based on 1 mg of its body surface area.

10049] Generally, camptathecin derivatives have a lactore ring structure, so it is considered that reduction of the drug effect occurs due to ring-opening of the lactore ring in the structure in the alkaline range, in consequence, it is desirable that a pharmacoutical composition containing a camptothecin derivative having a factore ring or a self-thereof is maintained within excitic range for the purpose of keeping the lactore ring under closed state. On the other hand, since the compound A or a saft thereof causes salting out under a strongly acidic condition of pH 2.0 or less, its solubility is considerably reduced. From two viewpoints of keeping closed state of factore ring and ensuring proper solibility of the compound, it is destrable that the pharmaceutical composition of the invention is maintained within a weakly acidic condition by formulating a pH-adjusting substance, in this connection, when the pharmaceutical composition is an acueous preparation, the term "a weakly acidic condition" as used herein means from about pH 3 to 5, and when the pharmaceutical composition is a recerved-dedpreparation, impeans that pH of an equeous solution prepared by dissolving in water is from about pH 3 to 5.

[0080] Though the pit-ladjusting substance is not particularly limited, with the proviso that it can maintain the phermaceutical composition of the invention within the weakly acidic range, an acidic substance and/or a basic substance, for example, can be effect. As the acidic substance, hydrochloric acidi, acetic acid, sodium acatorist, acid, acidic acidic

[0051] The jrl-adjusting substance is blended in such an amount that the lactonering of the camptothecin derivative or a salf thereof is kept under closed state and that 0.7 mg/ml or more, preferably 1 mg/ml or more, of the solubility of the camptothecin derivative or a salf thereof is separable solubine concentration at the time of the administration of the pharmaceutical composition. Illustratively, it may be such an amount that pH of the pharmaceutical composition can be kept within a weakly acidic condition, preferably an amount which can keep a pH of from 3.5 to 5.0, more preferably an amount which can keep a pH of from 4.0 to 4.5.

[0082] Also, it is destrable to further biend the pharmacoutical composition of the invention with a sugar annoin a sugar attend for the purpose of improving siability of the camptothecin derivative or a sait thereof. Exempler include maltose, glucose, lactose, saccharose, mannitol, incellol, galactose, ribose, xylose, mannose, sucrose, cellobse, relitiose, maltotices and the life, which may be used alone or as a combination of two or more. Among them, it is desirable to use maitose. Blending amount of the sugar and/or sugar about lei from 15 to 30 parts by weight, preferably from 25 to 75 parts by weight, more preferably 25 or 38 parts by weight, based on 1 part by weight of the camptothecind derivative or a sait thereof (in any form a hydrate or the like solved or the like observatives.)

[0953] As a preparation capable of providing for medicinal use, it is desirable to keep the drug content at 80% by weight or more, under usual storage conditions, at the time of its preparation, Also, it is desirable to keep impurities such as degraded products at a level of 3.5% by weight or less, more preferably 1% by weight or less, at the time of its preparation.

[0054] Since the compound A or a saft thereof is considerably unstable against heat and light, changes in appearance, generation of insolute foreign matter, reduction of the content and the like due, processly, to exidative degradation of the compound are observed when its severe treatment with heat and light is carried out. In consequence, overridit approach and the like sterilization methods which accompany heating are not suited for the pharmaceutical composition of the invention. In order to obtain a substantially sterilized condition, it is desirable to employ a method in which the pharmaceutical composition is prepared under asseptic condition, a method in which a filter sterilization-reasted a deutron of the pharmaceutical composition is made into a freeze-dried preparation, and the like. Particularly, the method for making a freeze-dried preparation is desirable. In addition, it is desirable for its preservation to use a container having standing ability. For example, brown visia a rath the like can be clied.

[0055] In addition, the pharmacoulted composition of the invention may exist aimply as a mixture of a composition of the invention may exist aimply as a mixture of a composition derivative or a salt thereof, a pt-hadjusting substance and, as occasion demands a sugar and/or a sugar alcohol, or it may also has an aqueous preparation, freeze-dried preparation or the like known properation form. Examples of the accounts preparation include aqueous injections prepared by filter-sterilizing the pharmaceutical composition, another accounts prepared by dissolving the pharmacountied composition one made into a freeze-dried preparation, and the like. Production mathed of the freeze-dried preparation is not particularly limited, and any method known by itself may be used.

[0056] The following describes the invention further in detail with reference to examples, but the invention is not imitted to them, in this connection, the compound AS or a salt thereof used in the least shown in Examples contains approximately 0.3% by weight of the compound AF or a salt thereof. The compound AF or a salt thereof and degraded products of the compound A or a salt thereof were combined and called "total analogous matter" in the following axiamples. Also, the concentration of the total analogous matter was indicated as a concentration converted to free form of compound AS.

Best Mode for Carrying Out the Invention

(Example 1) Stability of a freeze-dried camptothecin derivative (compound AS hydrochloride)

[0057] A 1 mg/ml aqueous solution of compound AS hydrochloride (molecular weight, 472) (a), a 1 mg/ml solution (1:40 by weight) of compound AS hydrochloride containing 4% by weight concentration of mannitol (b), and a 1 mg/ml solution (1:30 by weight) of compound AS hydrochloride containing 8% by weight concentration of matitose (c) were separately freeze-dride and then severe freatment with heat and sight was carried out to confirm changes in the content. Coloriess viels were used as the contenter.

[0058] As a result, it was revealed that the stability of compound AS is increased by the addition of a sugar or a sugar alcohol, and significant stability was observed particularly when maltose was added (Table 1).

Table 1. Stability of compound AS hydrochloride under freeze-dried condition

Freeze-dried product Storage condition 40°C, 75% R.H., 1 month	Weight % of compound AS based on the start time 91.4	b Weight % of compound AS based on the start time 101.9	C Weight % of compound AS based on the start time 104.0
60°C, 2 weeks	83.4	104.2	101.8
600,000 LUX:h	44.3	65.6	97.2

(R.H.: relative humidity)

(Example 2) Stability of a freeze-dried camptothecin derivative (compound AS methanesulfonete)

[0059] Mannito (a), meliciae (b) or lactose (c) was added to an aqueous solution (1.5 mg/ml as a concentration converted to free form) of compound AS methanesulfonate (hereinafter, the compound AS methanesulfonate (hereinafter, the compound AS methanesulfonate meligint 580) to the final concentration of 50 mg/ml (AS methanesulfonate mannitols-125 by year and AS methanesulfonate meligint), and pH was a methanesulfonate meligint), and pH was another and the severe treatment with another and light was carried out to confirm changes in the formation of analogous matter. Coloriese vials were used as the confiance.

[0060] As a result, it was revealed that the effect to inhibit analogous metter formation becomes higher when maltose or lactose is added than the case of the addition of manniot (Table 2).

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Table 2. Stability of compound AS methanesulfonate under freeze-dried condition

Freeze-dried	a (mannitol)	b (maltose)	c (lactose)
product			
	Weight % of	Weight % of	Weight % of
Storage	total	total	total
condition	analogous	analogous	analogous
\	matter	matter	matter
Starting time	0.43	0.45	0.40
60°C, 2 weeks	1.12	0.68	0.48
600,000 LUX-h	2.54	0.95	1.03

(Example 3) Stability of a freeze-dried camptothecin derivative (compound AS methanesulfonaire) (effect of the addition of acidic substance)

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[0061] Máltisse was added to an aqueous solution (1.0 mg/ml as a concentration converted to free form) of compound AS methanesulfonate to the final concentration of 50 mg/ml (AS methanesulfonate:mailcose=1:38 by weight), and pel-was adjusted to 4.0 with hydrochipro acid (a), sodium ascorbate (b) or sodium accatte (c). Each solution was freeze-dired and then severe healt treatment was carried out to confirm changes in the formation of analogous matter. Brown villa were used as the cennial matter.

[0062] As a result, if was revealed that the effect to inhibit analogous matter formation becomes higher when hydrochloric acid is added than the case of the addition of other acidic substances (Table 3).

Table 3. Effect of acidic substance on the stability of compound AS methanesulfonate under freeze-dried condition

Freeze-dried	a (hydrochloric	b (sodium	c (sodium
product	acid)	ascorbate)	acetate)
	Weight % of	Weight % of	Weight % of
Storage	total	total	total
condition	analogous	analogous	analogous
	matter	matter	matter
Starting time	0.4	0.4	0.4
60°C, 2 weaks	0.5	2.6	11.4

(Example 4) Stability of a freeze-dried camptothecin derivative (compound AS methanesulfonate) (effect of the addition of mailtose)

[0063] Mathose was added to an aqueous solution (1.0 mg/ml as a concentration converted to free form) of compound A3 mothanasulfonate to the final concentration of 50 (A8) methanasulfonate.methose=1:38 by weight) or 100 mg/ml (A8 methanasulfonate.methose=1:77 by weight), and pit was adjusted to 4.0 with hydrochloric acid. Each estudion was freeze-drifted and then severe heaf treatment was carried out to confirm changes in the formation of analogous mariter Brown vides were used as the container.

[0064] As a result, it was revealed that difference in the mailtose blending ratio exerts influence upon the formation of analogous matter (Table 4).

Table 4. Effect of the adding amount of maltose on the stability of compound AS methanesulfonate under freeze-dried condition

Freeze-dried product	Maltose 50 mg/ml	Maltose 100 mg/ml
Storage condition	Weight % of total analogous matter	Weight % of total analogous matter
Starting time	0.34	0.50
40°C, 75% R.H., 1 month	0.52	1.36
50°C, 1 month	0.80	2.24

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(R.H.: relative humidity)

(Example 5) Stability of a freeze-dned camptothecin derivative (compound AS methanesulfonate) (effect of pH)

[0065] Maitose was added to an aqueous solution (1.0 mg/ml as a concentration convented to free form) of compound AS menhaneoutionate to the final concentration of 100 mg/ml (AS methaneoutionate-meltose=1.77 by weight), and p-tiwas adjusted to 5.5, 4.0 or 4.5 by adding hydrochioric soid. Each solution was freeze-dried and then severe heat treatment was curried out to confirm changes in the formation of enalogous matter. Brown vials were used as the container.

[0066] As a result, it was revealed that the effect to inhibit analogous matter formation becomes most high when pH is adjusted to around 4,5 (Table 5).

Table 5. Effect of pH on the stability of compound AS methanesulfonate under freeze-dried condition

Freeze-dried product	pH 3.5	pH 4.0	pH 4.5
Storage condition	Weight % of total analogous matter	Weight % of total analogous matter	Weight % of total analogous matter
Starting time	0.72	0.50	0.40
40°C, 75% R.H., 1 month	3,12	1.36	0.51
60°C, 2 weeks	7.52	3.13	0.75

(R.H.: relative humidity)

(Example 6) Stability of a freeze-dried camptothecin derivative (compound AS methanesulfonate) (effect of ph)

[0067] Maltose was added to an equecus sotution (1.0 mg/ml as a concentration converted to free form) of compound AS methanesulfonate maltoses 1.38 by weight), and pH was adjusted to 2.5, 3.0, 3.5 or 4.0 by adding hydrochloric soid. Each solution was freeze-order and then severe hest teatment was carried out to confirm changes in the formation of analogous matter. Colorless vials were used as the particular confirmation of analogous matter.

[0068] As a result, it was revealed that the effect to inhibit analogous matter formation becomes most high when pH is adjusted to around 4.0 (Table 6).

Table 6. Effect of pH on the stability of compound AS methanesulfonate under freeze-dried condition

Freeze-dried product	pH 2.5	pH 3.0	pH 3.5	pH 4.0
Storage condition	Weight % of total analogou s matter			
Starting time	1.05	0.42	0.27	0.23
60°C, 2 weeks	21.43	10.64	5.07	1.83

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(Example 7) Changes in pH of a freeze-dried camptothecin derivative (compound AS methanesulfonate) by freeze drying treatment

[0089] The pharmscattleat composition containing compound AS methanesulfonate was produced according to the formulation and production scale shown in Table 7 (AS methanesulfonatemaltoses1:19 or 1.38 by weight), and pit of the solution before freeze drying and pit of a solution propered by dissolving the proparation after freeze drying in water to the same concentration of the solution before freeze drying were measured. As a result, it was revealed that the pit hardly changes by freeze drying treatment.

Table 7.

Production scale	Formulation		pH Before freeze drying	pH After freeze drying
28.0 L	Compound AS Maitose Hydrochloric acid proper amt. Water	2 mg 50 mg totsil vol. 1 ml	3.87	3 83
28.0 L	Compound AS  Mallose  Hydrochloric acid proper amt.  Water	2 mg 50 mg lotal vol. 1 ml	3.73	4.60
90.0 L	Compound AS Maltese Hydrochloric acid proper amt Water	2 mg 100 mg total vol. 2 ml	3.85	3.97

(Example 8) Stability of a freeze-dried camptothecia derivative (compound AS methanesulionate) (long term stability)

[0070] A 1.4 kg portion of maltose and 73 g (56 g as converted to fire form) of compound AS methanesultonate was dissolved in 22.1 of water (AS methanesultonate mailtose=1:18 by weight). This solution was adjusted to a pH range of from 3.5 to 3.9 by adding proper amount of hydrochioric acid; filled up to 28 L by adding water, followed by the steribility, and then dispensed into vials. After freeze drying, this was stored under a condition of 5°C or 28°C with a relative humidity of 50%, and then dispensed into water to the same concentration of the solution before freeze drying to measure pH. Also, changes in the formalion of analogous matter wave confirmed. Colorless vials were used as the container.

[9071] As a result, the pH after freeze drying varied from pH 3.7 to 4.8 including experimental error under each

storage condition (Table 8)

[9072] Since formation of the total analogous matter until 37 months was 0.33% or less as weight % of the total analogous matter, long term stability of the compound A5 methanesulfonate freeze-dried preparation was confirmed (Table 8).

Table 8. Long term stability of the compound AS methanesulfonate under freeze-dried condition

Freeze-dried product storing condition	5°C		25°C, 60% R.H.	
Storage period	Total analogous matter weight %	PH	Total analogous matter weight %	рĦ
Starting time	0.33	3.8	0.33	3.8
1 month	0.32	3.9	0.33	3.9
3 months	0.33	3.9	0.33	3.9
6 months	0.33	3.7	0.33	3.7
9 months	0.33	4.0	0.33	4.0
12 months	0.33	3.9	0.33	4.0
24 months	0.33	4.1	0.33	4.3
30 months	0.33	4.6	_	-
37 months	0.32	3.7	0.33	3.9

(R.H.: relative humidity)

(-: not tested)

industrial Applicability

[0073] As described above, the pharmaceutical composition of the inventors can be used as a camptothecin derivative preparation having excellent stability and solubility.

## Claims

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- A pharmaceutical composition which contains (9S)-1-amino-9-eithyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H, 2H-benzo[de]pyrano[3',4':6.7]indoilizino[1,2-b]quinoline-10,13(8H.15H)-dione or a salt thereof and a pH-adjusting substance.
- A pharmaceutical composition which contains (1S,9S)-1-amino-9-shtyl-6-fluoro-2,3-dithydro-9-hydroxy-4-methyl-11.12H-benzo(de)pyrangi3-8-0.7jindoilzing[1,2-b]quinolino-10,13(6H,15H)-dione or a set thereof end a pH-ad-justing substance.
- A pharmaceutical composition which contains (9S)-1-amino-9-einly1-5-fluoro-2,0-dihydro-9-hydroxy-4-metryl-1H.
   12H benzeldajpyrano(3/4\*6,7)indolfizno(1/2-b)quinoline-10,1(9H,15H)-dione or a sait thereof, a pH-adjusting substance and one or more of supera and/or sucer slochels selected from the following orous.
  - mallose, glucose, lactose, saccharose, mannitol, inositol, galactose, ribose, xylose, mannose, sucrose, cellobiose, raffinose and maltotriose.
  - A pharmaceutical composition which contains (15, 85)-1-amino-6-ethyl-5-iluoro-2,3-diffydro-9-hydroxy-4-methyl-1H,12H-benz-qleiplyrand(3'.4' 5.7]indoizind(12-b)quinosina-10,13(94,15H)-dinos or a satithereof, a ph-adjusting substance and one or more of sugars and/or sugar alcohols selected from the following group:

maliose, glucose, lactose, saccharose, mannitol, inositol, galactose, ribose, xylose, mannose, sucrose, collobiose, raffinose and maliotriose.

- A pharmaceutical composition according claim 3 or 4, wherein blending amount of the sugar end/or sugar alcohol
  is from 15 for 80 parts by weight based on 1 part by weight of (98)-1 amon-9-einyt-5-fluor-o-2,3-diflydrio-9-hydroxy4-methy-111,1291-bonzo(dejpyrano(3',4-8);flindoiring(2;a-b)qiunofine-1,01(3)(4)-15)-dione or a sait thereof
- A pharmaceutical composition according claim 3 or 4, wherein blending amount of the sugar and/or sugar alcohol
  is from 261o 75 parts by weight based on 1 part by weight of (85)-1-emits-9-ethyl-5-fluore-2, 3-dihydro-9-hydroxy4-methyl-11-1,24-hospicelpsynarol(5/4-7)findokipril-2,2-bigluintiper-1,01(3(94):157)-tipene or a satt hereof.
  - A pharmaceutical composition according any one of claims 1 to 6, wherein said pH-adjusting substance is hydrochloric acid.
- A pharmaceutical composition which contains (9S)-1-arrano-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H, 12H-banzo(digipyrano[3',4:6,7]indelizino[1,2-b]quinoline-10,13(9H,15H)-dione or a salf thereof, hydrochloric acid and maltose
- 9. A pharmaceutical composition which contains (19,98)-1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-11-12H-benzoldelpyrano(3',4':8,7]indollzino(1,2-b]quinolline-10,13(8H,15H)-dione or a satt thereof, hydrochloric acid and matiose
  - 10. A pharmaceutical composition according claim 8 or 9, wherein blending amount of mailose is from 15 to 80 parts by weight based on 1 part by weight of (85) - 1 amino-9-ethyt-5-fluoro-2,3-dinydro-9-hydroxy-4-methyt-1H,12Hbenzo(delpyman(9) 41-65 [indexized], 2-gluincline-10,16(9),16H)-dono or a sett thereof.

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- A pharmaceutical composition according claim 8 or 9, wherein blending amount of mailtose is from 25 to 75 parts by weight based on 1 part by weight of (69)-1-amino-8-einly-6-fluoro-2,3-dilhydro-9-hydroxy-4-methyl-1H,12Hben 70(de)pyrano(3/4-6,7)Indiokino(1/4-2)-pilunioline-10,12(H-15H)-dione or a salt thereof.
- A pharmaceutica composition which contains (9S)-1-amino-9-ethyl-5-fluoro-2, 3-dihydro-9-hydroxy-4-methyl-1H. 12H-benzo(de)pyrano(3',4's,7)indolizno(1,2-b)quinoline-10,13(9H,15H)-dione hydrochloride or methanesulfonate, hydrochloric adid and methose.
- A pharmaceutical composition which contains (1S,9S)-1-amino-9-athyl-5-fluoro-2,3-dithydro-9-hydroxy-4-mathyl-1H.12H-benzo[de]pyrano[3:4:3,7]indolizino[1,2-b]quinoline-10,13(9H,15H)-dilone hydrochloride or methanasulonate, hydrochloric acid and matosa.
- 14. A pharmaceutical composition according claim 12 or 13, wherein blending amount of maltose is from 15 to 80 parts by weight based on 1 part by weight of (95)-1-amino-9-eithyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H, 12H-benzo(de)pyrano[3,4:6,7]indollizino[1,2-b]quinoline-10,13(9H,16H)-dione hydrochloride or methanesutfonate.
- A pharmaceutical composition according claim 12 or 13, wherein blending amount of malices is from 25 to 75 parts by weight based on 1 part by weight of (9S) -1-emino-9-ethyl-5-fluoro-2,3-diflydro-9-hydroxy-4-methyl-11i, 12H-benzo(de)pyrano(5',4':6,7)mdoliz-no(1,2-b)quinoilne-10,13(8H,15H)-dione hydrochloride or methanasulfonate.
  - 16. The pharmaceutical composition according to any one of claims 1 to 15, wherein pH is a weekly addic condition.
    - 17. The pharmaceutical composition according to any one of claims 1 to 15, wherein pH is from 3.5 to 5.0.
  - 18. The pharmaceutical composition according to any one of claims 1 to 15, wherein pH is from 4.0 to 4.5.
- A pharmaceutical composition which contains (9S)-1-amino-9-ethyl-5-fluoro-2,3-diffydro-9-hydroxy-4-methyl-1H,
  12H-benzo[de]byrano[3'.4'6.7]indoilizinoi[1,2-b]quinoiline-11,13(9H,15H)-dione methenseutifonato, hydrochloric
  acid and mattose, wherein blending amount of maltose is 25 or 38 parts by weight based on 1 part by weight of
  (9S)-1-amiso-9-ethyl-5-fluoro-2,3-diffydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4'8.7]indoizino

II 2-blauinaline-10.13/9H.15H)-dione methanesulfonate, and nH is from 4.0 to 4.5.

- 20. A pharmaceutical composition which contains (1S.9S)-1-amino-9-ethyl-5-fluoro-2.3-dihydro-9-hydroxy-4-methyl-1H.12H-benzo(delevrano(3',4'.6,7)indolizmo(1',2-b)quino(ne-10,13(9H,15H)-dione matnanesulfanate hydrochicno acid and multiose, wherein blending amount of meltose is 25 or 38 parts by weight based on 1 part by weight (95)-1-amino-9-ethyl-5-fluoro-2.3-dihydro-9-hydroxy-4-methyl-1H 12H-benzoideloy/anol3-4';6,7lindolizino [1,2-b]quinoline-10,13(9H,15H)-dione methanesulfonate, and pH is from 4.0 to 4.5.
- 21. A freeze-dried preparation which contains the pharmaceutical composition described in any one of claims 1 to 20,
- 22. An aqueous preparation prepared by dissolving the freeze-dried preparation described in claim 21.
- 23. A process for producing a freeze-dried preparation described in claim 21 which comprises adjusting an aqueous solution containing (95)-1-amino-9-athyl-5-fluoro-2.3-drhydro-9-hydroxy-4-mathyl-1H, 12H-benzoideloyranoi3',4': 6,7 indolizinoi 1,2-biquinoline-10, 13(9H, 15H)-dione or a salt thereof to a weakly acidic condition, and then freezedrying the resulting solution.
- 24. The process according to claim 23 which comprises steps of:

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- (1) preparing an agueous solution by dissolving sugars and/or sugar alcohols in water.
  - (2) dissolving (9S)-1-emino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzpfgelpyranol3',4";
  - 6.7|indolizino(1,2-b)quinofine-10,13(9H,15H)-dione or a salt thereof.
  - (3) adjusting pH to a weakly acidic condition with a pH-adjusting substance; and
  - (4) dispensing the resulting solution into yial after filter-sterilizing it, and followed by freeze-drying it.
- 25. The process according to claim 29 or 24 which comprises steps of:
  - (1) preparing an aqueous solution by dissolving mallose in water:
  - (2) dissolving (1S,9S)-1-emino-9-etryl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(de)pyrano [3',4':6,7]indolizino[1,2-b]quinoline-10,13(6H,15H)-dione methanesulfonate;

  - (3) adjusting o'H to from 3.5 to 5.0 with a pH-adjusting substance; and
  - (4) dispensing the resulting solution into vial after filter-sterilizing it, and followed by freeze-drying it.
- 26. Use of (9S)-1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(de)pyrano(3',4':6,7lin-25 dolizino[1.2-b]quinoline-10,13(9H,15H)-dione or a salt thereof for producing the pharmaceutical composition described in any one of claims 1 to 20, the freeze-oried preparation described in claim 21 and the aqueous preparation described in claim 22.
- 27. Use of #15.95)-1-amino-9-ethyl-5-fluoro-2.3-dihydro-9-hydroxy-4-methyl-1H.12H-benzo[delpyranol3'4',6.7lin-40 dollating[1,2-b]quinoline-10,13(9H,15H)-dione methanesulfonate for producing the pharmaceutical composition described in any one of claims 1 to 20, the freeze-dried preparation described in claim 21 and the aqueous preparation described in claim 22

# Amended claims under Art, 19.1 PCT

- 1. A pharmeceutical composition which contains (9S)-1-emino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H.12H-benzo[de]pyranoi3',4':6,7[indpitzino[1,2-b]quinoline-10,13(9H,15H)-dione or a salt thereof and a pH-adlusting substance
- 2. (Amended) A pharmeceutical composition which contains (98)-1-amino-9-ethyl-5-fluore-2,3-dihydro-9-hydroxy-4-methyl-1H.12H-benzojdejpyranc(3'.4'.6,7)indolizinoj1,2-bjquinoline-10,13(9H,15H)-dione or a sait thereof, a pH-adjusting substance and one or more of sugars and/or sugar alcohols selected from the following group.
- maltose, glucose, lectose, saccharose, mannitol, inositol, galactose, nibose, xylose, mannose, sucrose, pellobiose, raffinose and maltotriose.
- 3. (Amended) A pharmaceutical composition which contains (9S)-1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H.12H-benzolde/pyranol3\*, 4\*:6,7lindolizinol1,2-blouinoline-10.13(9H.15H)-dione or a salt thereof, a

pH-adjusting substance and one or more of sugars and/or sugar alcohols selected from the following group, wherein bleeding amount of the sugar and/or sugar alcohol is from 15 to 80 parts by weight based on 1 part by weight of 695-1 acmino-9-ethyl-6-fluore-2,3-dhydro-9-hydroxy-4-methyl-1H.12H-benzo(de)pyrano(3'.4'.6,7)indolazino 11.2-b)quinolina-16,13(9H.15H)-done or a sait thereof.

malfose, glucose, lactose, saccharose, mannitol, inositol, galactose, ribnse, xylose, mannose, sucrose, celibbiose, raffinose and maltotriose.

4. (Amended) A pharmaceutical composition which contains (9S)-1-amino-9-eitlyl-5-fluoro-2,3-ditydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3]-4: 6.7 jindolizino[1,2-b]quinoline-10,13[9H-15H-y-idone or a salt thereof, a pH-adjusting-substance and one or more of sugare and/or sugar actions use located from the following group, wherean blending amount of the sugar and/or sugar alcohols selected from the following group, when being amount of the sugar and/or sugar alcohol is from 25 to 75 parts by weight based on 1 part by weight of (9S)-1-amino-9-eithy-fluoro-8-jindroxy-4-methyl-1H.12H-benzo[de]pyrano[3',4':6.7 jindolizino [1,2-biquinoline-10,18]9H.15H-diene or a salt thereof.

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maltose, glucose, lactose, saccharose, mannitol, mositol, galactose, ribose, xylose, mannose, sucrose, cellobiose, raffinose and maltotriose.

- (Amended) A pharmaceutical composition which contains (16,65)-1-amino-9-etryl-6-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H.12H-benzo(sdjpyrano)3.4:6,7jindoilz:no[1,2-b)quinolina-10,13(9H,15H)-dione or a salt thereof and a pH-edjusting substance.
- 6. (Amended) A pharmaceutical composition which contains (15,98)-1-amino-9-cityl-5-fluoro-2,9-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(dejpyrano[3',4:8,7]indolizing[1,2-b]quinoline-10,13(9H,15H)-done or a sail thereof, a pH-adjusting substance and one or more of sugars and/or sugar alcohols selected from the following granultose, glucose, factose, saccharose, mannifol, inositol, galactose, ribose, xylose, mannose, aucrose, celloises, raffinose and maltitotion.
- 7. (Amended) A pharmaceutical composition which contains (15,98)-1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(be)pyrano[3'.4':6,7]indolkino[1,2-b]quinoline-10,13(9H,15H)-dione or a sall thereof, a pH-adjusing substance and one or more of sugars and/or sugar alcohols selected from the following group, wherein blending amount of the sugar and/or sugar alcohol is from 15 to 50 parts by weight based on 1 part by weight of (15.95)-1-amino-9-ethyl-5-luoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(de)pyrano[3'.4':6,7]in-oklizino[12-0]-juliunioline-10,13(9H,15H)-dione or a sait hereof.

maitose, glucose, lactose, saccharose, mannitol, inositol, galactose, ribose, xylose, mannose, sucrose, cellobiose, raffinose and maltotriose.

8. (Amended) A pharmaceutical composition which contains (1S,9S)-1-amino-0-eithyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-11-h;2P-banzo(falpyrano[3,4':6,7]indolliz-nof[,2-b]quinolline-10,13(9H,15H)-dione or a salt thereo, of, a pH-adjusting substance and one or more of sugars anchor sugar alcohols selected from the following group, wherein blending amount of the sugar and/or sugar alcohol is from 25 to 75 parts by weight based on 1 part by weight of (1S,9S)-1-amino-0-eithyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':6,7]indollzinol 12-biguinoline-10-31(9H):15H-bigne or a satt harmon.

maitose, glucuse, lactose, seccharose, mannitol, inositoi, galactose, ribose, xylose, mannose, sucrose, cellobiose, raffinose and maitotnose.

- (Amended) A pharmaceutical composition according any one of claims 1 to 8, wherein said pH-adjusting substance is hydrochloric acid
- (Amended) A pharmaceutical composition which contains (95):1-amino-9-eithyl-5-fluoro-2,0-dihydro-8-hydroxy-4-methyl-1H,12H-benzo[dejyrano[3-4:5.7]indolizino[1,2-b]quinoline-10, 13(9H,15H)-dione or a salt thereof, hydrochloric acid and maltuse.
- 11. (Amended) A pharmacoutical composition which contains (98)-1-amino-9-ethyl-5-fluoro-2,3-dihydro-3-hydroxy-4-nethyl-1-12t-baro(dejpyrano(3'-4')3-fjadolzina(1,2-b)quinoline-10,13(9H,15H)-dino or a east thereof, hydrochloric acid and maltose, wherein biending amount of maltose is from 15 to 80 parts by weight based on 1 part by weight of (85)-1-amino-9-ethyl-5-fluoro-2-3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(dejpyrano(3'-4'-15-fluoro-2-3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(dejpyrano(3'-4'-15-fluoro-10-fl
- 12. (Amended) A pharmaceutical composition which contains (9S)-1-amino-9-ethyl-5-fluoro-2.3-dihydro-9-hy-

stoxy-4-methyl-1H, 12H-benzo(delpyrane[3,4\*6,7]indoitrino[1,2-b]quinoline-10,13(9H,15H)-dione or a salt thereof, hydrocriticis acid and methose, wherein blending amount of methose is from 25 to 75 parts by weight based on 1-part by weight of (95)-1-amino-9-eihyl-5-fluore-2,3-eihydro-9-hydroxy-4-methyl-1H,12H-benze(delpyrane[3',4': 6-7]indoitzinof(3-2-b)quinoline-10,13(9H,15H)-dione or a salt thereof.

(Arnended) A pharmacountcal composition which contains (15,95)-1-amino-9-ethyl-5-fauoro-2,3-ditydio-9-hydroxy-4-methyl-11h, (21-hoarze(de)pyrano(3,46,7)indoitzino[1,2-b]quinoline-10,13(8+1,15+)-dione or a selt there-chi, hydrochine add and malkose.

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- 14. (Amendesi) Apharmacoutical composition which contains (15,05): 1-amino-9-ethyl-5-fluoro-2,3-dihydro-6-thyl-drony-4-methyl-1+1,12H-benzo[de]pyrano[3'.4' 6,7]indoilizino[12-b]quinoline-10,13(9H,15H)-dione or a sall thereol, hydrochiorio acid and malitose, wheren biending amount of malitose is from 15 to 80 parts by weight based on 1 part by weight of 15,95)-1-amino-9-ethyl-6-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[5'.4'0.7]indoilizino(12-b)quinoline-10,13(9H,15h)-dione or a sall thereof.
- 15. (Amended) A pharmaceutical composition which contains (15,85)-1-arrano-9-ethyl-6-fluoro-2,3-dihyaro-9-hy-cray-4-methyl-1H,12H-benzo(de)pyrano[3',4':8,7]Indolizino(1,2-b)quinciline-10,13(9H,15H)-dione or a satisfiered, hydrochloric acid and mailtose, wherein blending amount of mattose is from 25 to 75 parts by weight by the physical production of the physical physical production of the physical phys
- (Amended) A phermaceutical composition which contains (9S)-1-amino-9-shlyl-5-fluore-2,3-dihydro-9-hydroxy-4-methyl-1H-12H-benze)dejpyrano(3,4'-8,7jindeizino(1,2-b)jquinolino-10,13(9H,15H)-drone hydrochloride or matenaesulinolate, hydrochloride add and mallose.
- 17. (Amended) A pharmaceutical composition which contains (9S)-1-amino-9-shyld-fluore-2,3-dihydro-9-ry-droxy-4-methyl-1H,12H-benzo[de]pyrang[3]:46,7]indol[zind]1,2-b]unolinia-1,013(bH,15H)-dione hydrochloric and and maltose, wherein blending amount of maltose is from 15 to 80 parts by weight based on 1 part by weight of (9S) -1-amino-9-shyl-5-fluore-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrang[3]:47,8-fluolipiten]1,2-fluolipiten[1-1,3]-fluolipiten]1,3-fluolipiten[1-1,3]-fluolipiten]1,3-fluolipiten[1-1,3]-fluo
- 18. (Amended) A pharmaceutical composition which contains (193)-1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(de[pyrano]3,4\*:6,7[indoldzino]1,2-b]quinoline-10,13(9H,15H)-dione hydrochloride or methanesutionate, hydrochloride acid and malitose, wherein blending amount of melitose is form 25 to 75 parts by weight based on 1 part by weight to (193)-1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(de[pyrano]3,4\*\*-6,7[indoldzino]1,2-b]quinoline-10,13(9H),15H-dione hydrochloride or methanesutionation.
- (Amendiad) A pharmaceutical composition which contains (15,95)-1-amino-9-athyl-5-fluoro-2,3-dilhydro-9-hydroxy-4-mothyl-1H,12in-benz/delpyrano[3,4:5.7]holoilzing[1,2-b]quinoline-10,13(9H,15H)-dione hydroxhlorise or meihanesuffonate, hydroxhlorise acid and mallose.
- 20. (Amended) A pharmaceutical composition which contains (1S,98)-1-amino-9-etnyl-5-fluoro-2.3-dilhydro-9-thy-croxy-4-methyl-1-H, 12ft-benze]delpyrane(3,4%,7)incoluzino] (1,2-b)quinolina-10,13(9i-1,5ft)-dione hydrochloride or mehianesumonione and and matiose, wherein blending amount of matiose is term 15 to 8 part by weight of (1S,98)-1-amino-9-ethyl-5-fluoro-2,3-dilhydro-9-hydroxy-4-methyl-1-H, 12ft-benze(delpyranol)3,4-6,7)indolizion[1,2-b)quinolizion[1,2-b)quinolizion[1,2-b)quinolizion[1,2-b)quinolizion[1,2-b)quinolizion[1,2-b)quinolizion[1,3-
- 21. (Amended) A pharmaceutical composition which contains (15,95) 1-amine-9-ethyl-5-fluoro-2,3-dilhydro-9-hydroxy-4-metryl-1H.12H-benzo[de]pyrano[3,4's.7]indoi:izne[1,2-b]junioine-0.13[6]-f,15H-dione hydrochlorice or methanessulforate, hydrochloric acid and maltose, wherein blending amount of maltose is form 25 to 75 perts by weight passed on 1 pert by weight of (15,95)-1-amine-9-ethyl-5-fluoro-2,3 dihydro-9-hydroxy-4-metryl-1H.12H-benzo[de]pyrano[3,4's.9,7]indoi:izne[1,5]-1-amine-9-ethyl-15-H-dione hydrochloride or methanessulforated.
- 22. (Amended) The pharmaceutical composition according to any one of claims 1 to 21, wherein pH is a weakly acidic condition.
- (Amended) The pharmaceutical composition according to any one of claims 1 to 21, wherein pH is from 3.5 to 5.0.

- 24. (Amended) The pharmaceutical composition according to any one of claims 1 to 21, wherein pH is from  $4.0 \ 6$ –4.5.
- 25. (Amended) A pharmaceutical composition which contains (98):1-amino-9-airly/s-future-2,3-ditydro-6-ty-croxy-4-methyl-1H,12H-benzo(de)pyrano(3,416,7]ndoizino(1,2-b)quinoiline-10,13(9H,15H)-dione methanesutioneus, hydrochloric acid and maltise, wherein blending amount of maltices is 25 or 38 parts by weight based on 1 part by weight of (95):1-amino-9-ethyl-6-fluoro-2,3-ditydro-9-hydroxy-4-methyl-1H,12H-benz-(de)pyrano(3',4'-5-7)middizino(1,2-b)quinoline-10,13(9H,15H-dione methanesutionata, and bH is form 4.0 to 4.5.
  - 26. (Amended) A pharmaceutical composition which contains (15,93) 1-amino-9-cityl-5-fluoro-2,3-dinydro-9-hydroxy-4-methyl-11+,12H-benzo(disjpyrano(3),418.7]indoizino(1,2-b)quinoline-10,10(9H,15H)-cione metranassidonate, hydrochione acid and maltiose, wherein blending amount of maltiose is 25 or 36 parts by weight basesidon 1 part by weight bendered by hydrochione-4-methyl-11+,12H-benzo(de)pyrano(3',4'8-7)indoizino(1,2-b)quinoine-10,13(9H,15H)-dione methanasulfonate, and H is from 4,0 to 4,5.
    - 27. (Amended) A freeze-dried preparation which contains the pharmaceutical composition described in any one of claims 1 to 26.
    - 28. (Amended) An aqueous preparation prepared by dissolving the freeze-dried preparation described in claim 27.
    - 29. (Amended) A process for producing a freeze-diled preparation described in claim 27 which comprises adjusting an aqueous solution containing (66):1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(de) pyrano(3'.4':6,7 |incializino(1,2-b)quinoline-10,13(9H,15H)-done or a salt thereof to a weakly acidic condition, and then freeze-drying the resulting solution.
    - 30. (Amended) A process for producing a freeze-dried preparation described in claim 27 which comprises adjusting an aqueous solution containing (15,95)-1 amino-0-ethyl-6-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo (delpyrano(3'.4'i.5.7)indoixino(1.2-b)quinoiine-10.13(9H,15H)-dione or a salt thereof to a weakly acidic condition, and then freeze-drying the resulting solution.
    - 31. (Amended) The process according to claim 29 or 30 which comprises steps of:
      - (1) preparing an aqueous solution by dissolving sugars and/or sugar elephols in water:
      - (2) dissolving (9S)-1-emino-9-ethyl-5-fluoro-2.3-dihydro-9-hydroxy-4-methyl-1H, 12H-benzolde]pyranol3',4';
      - 6.7lindolizino[1,2-b]guinoline-10,13(9H,15H)-dione or a salt thereof;

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- (3) adjusting pH to a weakly acidic condition with a pH-adjusting substance; and
- (4) dispensing the resulting solution into vial after filter-sterilizing it, and followed by freeze-drying it.
- 32. (Amended) The process according to claim 29 or 30 which comprises steps of:
  - (1) preparing an aqueous solution by dissolving sugars angler sugar alcohols in water.
  - (2) dissolving (1S,9S)-1-amino-9-ethyl-5-fluoro-2.3-dihydro-9-hydroxy-4-methyl-1H,12H-benzoldelbyranoi3',
  - 4':6.7 indolizino(1.2-b)quinoline-10,13(9H,15H)-dione or a salt thereof;
  - (3) adjusting pH to a weakly acidic condition with a pH-adjusting substance; and
  - (4) dispensing the resulting solution into vial after filter-sterilizing it, and followed by freeze-drying it.
  - 33. (Amended) The process according to any one of claims 29 to 32 which comprises steps of
    - (1) preparing an aqueous solution by dissolving maltose in water;
    - (2) dissolving (1S,9S)-1-amino-9-ethyi-5-fluoro-2.3-dihydro-9-hydroxy-4-methyi-1H,12H-benzo(de)pyrano(3',
    - 4'8,7|incolizino[1,2-b]quinoline-10,13(9H,15H)-dione methanesulfonate,
    - (3) adjusting pH to from 3.5 to 5.0 with a pH-adjusting substance; and
    - (4) dispensing the resulting solution into vial after filter-sterilizing it, and followed by freeze-drying it.
- 34. (Amended) Use of (9S)-1-amino-9-eithyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo(de)pyrano [3'.4'8.7]indoilizino[1,2-b]quinoline-10,13(9H,15H)-dione or a salt thereof for producing the pharmaceutical composition described in any one of claims 1 to 26, the freeze-dried preparation described in claim 27 and the aqueous preparation described in claim 28.

35. (Amended) Use of (18,95)-1-amino-9-ehyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H.12H-benzo(de) pyrano(3,4\*6.7)indibizindi;12-biguindihe-10,13(9H,15H)-dione methanasulfonate for producing the pharmaceutical composition described in any one of claims 1 to 26, the freeze-dried preparation described in claim 28.

D.

# INTERNATIONAL SEARCH REPORT

International application No.

		PCT/	/JP01/02982
	SSIFICATION OF SUBJECT MATTER COL AG1K31/4745, 47/04, 47/26	5, 9/19 // A61P3S/00, C	070491/22
Assording	to International Patrot Classification (IPC) or to both	national classification and IPC	
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Minimum .	documentation restrict feliasification system followersCl AS1K31/4745, 47/04, 47/26	d'hy elessification symbols) , 9/19 // A61935/00, CC	70491/22
Documents	ntion searched other than apparent documentation to t	the extent that such documents are include	led in the fields searched
	data base consulted during the international search (naz LUS (STN), MEDITIVE (STN), EMBAS!		soutch terms used)
c. Doct	JMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with industrian, where s		Relevant to claim No.
Х	SP, 737686, Al (Dailchi Selyak 16 October, 1996 (16.10.96) & JP, 8-337584, A	ra EG.),	1-27
X	JP, 2000-44567, A (Daiichi Pha 15 February, 2000 (15.02.03), sepacially, page 5, right column example 1 (Family: none) & Datebase CAPLUS on STM, America (Columbus, Ohio, USA), AN.192:	; Par. No. [0027]; working in Chemical Society (ACS)	9
A	EP. 495431, Al (Dadioh) Pharme 22 July, 1992 (22.07.92) 4 JP. 5-59061, A 6 US, 5637 4 US, 5658920, A 6 US, 5770 8 US, 5834476, A	7770, A	1-27
	tr documents are listed to the continuation of Rex C.	See parent family annex.	
"A" docum nunside "E" tatfiler niste "L" docum nisted is special "O" docum meant "P" docum	I emagories of sizet decreasance.  The many fine of sizet decreasance and deliver of sizet which is not not look or to practicular extensions are sized on the sizet of sizet which is not not look or to practicular extensions.  The sizet of sizet is sized to size the sizet of sizet sizet of sizet which is not practice of sizet sizet of sizet	The distribution of the state of course published after the circle of the and not in condition will consider a state of the circle of the and not in condition with construction of comment of permission reduceage, it considered solves or council the collection of the concerned in Statem and continuent of particular reference; it considered with one or stores often; considered with one or stores often; considered with one or stores often; committeed for first gardens are a permission for first gardens are a permission of the statement patterns of the same patterns of the statement of the same patterns of the statement of the statement of the same patterns of the statement of the	is the supplication but cited to adentying the invention and continue to the control to desert to investigate and are the colorest investigate cannot be and desertants, such and desertants.
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